

Appln. No. 09/864,873
Response dated September 17, 2003
Reply to Office Action of June 17, 2003

REMARKS

Claims 1 and 3-10 are pending in the instant application. In the Office Action mailed June 17, 2003, claims 1 and 3-10 were rejected. Applicants respectfully request favorable reconsideration of the rejections and allowance of the present application in view of the remarks presented herein.

The June 17, 2003 Office Action

Objection and Rejections withdrawn

In response to the Applicants' Amendment filed March 31, 2003, the Examiner withdrew the objection to the specification, and the rejections of the claims under 35 U.S.C. §112, second paragraph and 35 U.S.C. §102(b), set forth in the previous Office Action.

Applicants acknowledge and appreciate the withdrawal of these objections and rejections.

Examiner's rejection under 35 U.S.C. §103

In the June 17, 2003 Office Action, the Examiner rejected claims 1 and 3-10 under 35 U.S.C. § 103 as being obvious over Michienzi, et al. (Nucleic Acids Symposium Series No. 41, pp.211-214, 1999), in view of Browning, et al. (J.Virol. 73(6):5191-5195, 1999) and Stauber, et al. (Virology 252, pp. 126-136, 1998). Specifically, the Examiner stated that Michienzi, et al. teach a nucleolar delivery system for delivery of a Rev decoy wherein the delivery system comprises a Rev decoy sequence that has replaced an apical loop of U16snoRNA and a C/D box. According to the Examiner, Michienzi, et al. further disclose wherein this decoy is expressed from a vector in a cell under control of a pol III promoter. The Examiner acknowledged that Michienzi, et al. do not teach a Tat decoy comprised in their nucleolar delivery system.

The Examiner asserted that Browning, et al. teach a Tat decoy sequence comprising SEQ ID NO: 12 and that Stauber, et al. teach that HIV Tat protein is active in the nucleolus. The Examiner then concluded that it would have been obvious to one of ordinary skill in the art to substitute the Rev decoy sequence in the Michienzi nucleolar delivery system with a Tat decoy sequence as taught by Browning, to provide a vector effective to deliver the Tat decoy to the nucleolus because Rev and Tat were both known to be functional in the nucleolus. According to the Examiner, one of skill in the art would have been motivated to substitute the Tat decoy taught by Browning, et al. for the Rev

decoy taught by Michienzi, et al. to make a chimeric RNA for delivery of Tat (sic) to the nucleolus because, in the Examiner's view, Michienzi, et al. teach that this system is effective to deliver a decoy to the nucleolus to investigate the function of the protein which binds to the decoy and Stauber, et al. teach that Tat has a role in the nucleolus. The Examiner stated that one of ordinary skill in the art would have been motivated to make the claimed chimeric Tat decoy in order to further define the role of Tat in the nucleolus and to provide a vector to deliver the Tat decoy taught by Browning, et al. to a cellular compartment where the target of the Tat decoy is active.

In response, Applicants respectfully traverse the Examiner's rejection. Contrary to the position taken by the Examiner, one of ordinary skill in the art at the time of the invention would not have been motivated to combine the cited references and arrive at the claimed invention. Applicants' claimed invention is directed to, *inter alia*, a chimeric RNA molecule for delivering an HIV TAR RNA to the nucleolus of a cell, comprising a snoRNA or a portion thereof which retains the ability of a snoRNA to localize in the nucleolus of a cell, and an HIV TAR RNA which binds HIV Tat protein. The nucleolus is a sub organelle within the nucleus of the cell. Prior to the Applicants' invention, Tat was believed to be nuclearly distributed, i.e., distributed throughout the nucleus, including the nucleolus. Therefore, there was no suggestion in the art to target a TAR element specifically the nucleolus to bind with Tat. There also would have been no expectation that such a decoy specifically targeted to the nucleolus would inhibit Tat activity and thus HIV replication to the extent shown in Figure 12.

The Examiner first cites Michienzi et al. in support of the obviousness rejection. As the Examiner acknowledges, the Michienzi reference does not refer at all to a Tat decoy. The reference instead relates to a nucleolar decoy of a protein known to be nucleolar-localized (Rev). The Browning reference cited by the Examiner refers to a Tat decoy sequence that is not nucleolar-targeted.

The Examiner stated that the Stauber reference teaches that "HIV Tat protein is active in the nucleolus" and that "Tat has a role in the nucleolus." However, the Stauber reference also fails to teach or suggest Applicants' claimed invention. The Stauber reference reveals instead that Tat is active in the nucleus and that nucleolar accumulation, which was observed only as a result of overexpression, "is not prerequisite for function." (See Abstract, and pages 127 and 132). Another

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conclusion of the Stauber reference is that Tat shuttles between the nucleus and the cytoplasm, and therefore may have potential to perform functions in the nucleus as well as the cytoplasm. However, the Stauber reference does not describe or suggest activity of Tat in the nucleolus, and thus a need to inhibit such Tat activity. The Stauber reference (on page 132, column 1), also appears to teach away from Applicants' claimed invention, stating that "the high proportion of nuclear Tat indicated that the affinity of Tat for the nucleolus was not as high as Rev's. This was supported by the finding that adding the nuclear export signal (NES) of Rev to Tat resulted in a predominantly cytoplasmic protein. The steady-state distribution of Tat-NES was cytoplasmic, suggesting nuclear export being more efficient than nuclear retention." The Stauber reference also states that "in stable cell lines expressing low levels of Tat-GFP, the protein was almost equally distributed throughout the nucleoplasm. During HIV-1 infection, the levels of Tat are most likely even lower, suggesting that nucleolar accumulation is not important for function but facilitated by overexpression." (Page 132, column 1). Therefore, if one of skill desired to inhibit Tat activity, the Stauber paper teaches first inhibiting Tat in the cytoplasm, and then the nucleus – but not in a specific sub organelle within the nucleus, the nucleolus.

Therefore, Applicants assert that no motivation existed at the time of the invention for selecting and combining the cited references to arrive at the claimed invention. To the contrary, the art at the time taught away from Applicants' claimed invention. Even knowing that Tat could localize in the nucleus as well as the cytoplasm, and even recognizing that overexpression results in nucleolar accumulation, nothing in the art suggests that it would have been reasonable to expect success in inhibiting Tat activity using a decoy targeted to a limited subset of the nucleus, the nucleolus. Accordingly, it is clear that Applicants' claimed invention would not have been obvious to one of skill in the art at the time the invention was made, and that the references cited by the Examiner fail to support her rejection. Applicants therefore respectfully request that the Examiner reconsider and withdraw the rejection of claims 1 and 3-10 under 35 U.S.C. §103.


In view of the above amendments and remarks, it is believed that the claims satisfy the requirements of the patent statutes, are patentable over the prior art, and fully address the Examiner's concerns as set forth in the June 17, 2003 Office Action. Reconsideration of the instant application

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and early notice of allowance are requested. The Examiner is invited to telephone the undersigned if it is deemed to expedite allowance of the application.

RESPECTFULLY SUBMITTED,					
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